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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,995	METCALFE, SUSAN MARIE	
	Examiner	Art Unit	
	JON M. LOCKARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-33* is/are pending in the application.

4a) Of the above claim(s) *24-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21-33* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/06, 11/14/08, 11/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Alignment*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 21-23 in so far as they are drawn to a method for inducing or regulating an immune response with an axotrophin polypeptide, in the reply filed on 14 November 2008 is acknowledged. The traversal is on the ground(s) that the search and examination of Groups I-II are not unduly burdensome to the Examiner. This is not found persuasive for the following reasons. It is noted this application is a national stage application and therefore U.S. restriction practice (i.e., independent/distinct, undue search burden) does not apply. The inventions of Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding special technical features for the reasons set forth at pg 3 of the previous Action (mailed 17 September 2008).

2. The restriction requirement is still deemed proper and is therefore made FINAL.

3. Claims 24-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 14 November 2008.

Status of Application, Amendments, and/or Claims

4. The Amendment filed on 03 July 2008 has been entered in full. Claims 1 and 6-8 have been cancelled, and claims 41-43 have been withdrawn from further consideration as discussed

supra. Therefore, claims 37 and 40-59 are pending, and claims 37, 40, and 44-59 are the subject of this Office Action.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on 31 July 2006, 14 November 2008, and 14 November 2008 have been considered by the Examiner.

Specification

6. The disclosure is objected to because of the following informalities: The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Appropriate correction is suggested.

Claim Objections

7. Claims 21 and 23 are objected to because of the following informalities: claims 21 and 23 are objected to for encompassing non-elected inventions, i.e., a polynucleotide (claims 21 and 23), and a substance that enhances the amount or activity of polypeptide expressed directly or indirectly by axotrophin (claim 23). Appropriate correction is suggested.

Claim Rejections - 35 USC § 112, 1st Paragraph (Scope of Enablement)

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting an adverse immune response in an individual or ex vivo cell population to an antigen, comprising administering to the individual or the ex vivo cell population an effective amount of an axotrophin polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:4, wherein the adverse immune response is inhibited after administration of the axotrophin polypeptide, does not reasonably provide enablement for a method of inducing or regulating, directly or indirectly, the immune response of an individual and/or ex vivo cell population to an antigen by using axotrophin or a polypeptide derived from axotrophin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

10. The specification's disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

11. The claims are drawn very broadly to a method of inducing or regulating, directly or

indirectly, the immune response of an individual and/or ex vivo cell population to an antigen by using axotrophin or a polypeptide derived from axotrophin. The specification teaches that the term "axotrophin" includes a reference to a polynucleotide or polypeptide sequence having at least 75% and preferably at least 90% sequence identity to an identifying sequence of axotrophin (See pg 1, lines 13-15), and the term "derived from axotrophin" includes, by way of example, anti-sense sequences including RNAi, whether single or multiple stranded, and small molecules binding to polypeptides or polynucleotides of axotrophin, including antibody especially monoclonal antibody, and reference to materials derived "directly or indirectly" from axotrophin includes any such polynucleotides or small molecules (See pg 2, lines 25-29). Thus, claims 21-23 have been broadly interpreted by the Examiner as reading upon variants of the axotrophin polypeptide, as well as materials derived from axotrophin as set forth *supra*. However, other than the axotrophin polypeptide comprising the amino acid sequence of SEQ ID NO:3 (mouse) or SEQ ID NO:4 (human), the disclosure fails to provide sufficient guidance and information regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claims. The disclosure has not shown (1) which portions of the polypeptide of SEQ ID NO:3 or SEQ ID NO:4 are critical to the activity of said axotrophin proteins; and (2) what modifications e.g., substitutions, deletions, or additions) one can make to SEQ ID NO:3 or SEQ ID NO:4 that will result in protein mutants or variants with the same function/activity as the proteins of SEQ ID NO:3 and SEQ ID NO:4.

12. The art teaches that little is known about the molecular and cell biology of axotrophin, also referred to in the art as MARCH-7, except that it lacks a transmembrane domain and appears to be cytoplasmic (See Muthukumarana et al. International Immunopharmacology.

6:1993-201, 2006). The state of the art is such that the relationship between the sequence of a protein and its activity is not well understood and unpredictable, and that certain positions in the sequence are critical to the protein's structure/function relationship and can only tolerate only relatively conservative substitutions or no substitutions.

13. The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions and still retain the activity of the polypeptides of SEQ ID NO:3 and SEQ ID NO:4.

14. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of

direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the phrase "an individual and/or ex vivo cell population". Without knowing whether the ex *vivo* cell population is from the same individual, resulting in a single method, or from a different individual, resulting in two separate methods, the metes and bounds of the claim cannot be determined.

18. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the claim recites the phrase "using axotrophin or a polypeptide or polynucleotide encoded by or derived from axotrophin". However, since the limitation does

not set forth any method steps, it is unclear what additional method steps are intended to be encompassed by the claim. Furthermore, the claim is indefinite because the claim does not have a step that clearly relates back to the preamble. For example, there is no step indicating that the axotrophin polypeptide results in the regulation of an immune response, nor is there guidance as to an amount of the active agent or desired outcome.

19. Claims 22-23 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (WO 02/070539 A2, published 12 September 2002).

22. Tang et al. teach an isolated human axotrophin polypeptide (See pg 210, SEQ ID NO:1612) that shares 100% sequence identity to SEQ ID NO:3 of the instant application (See attached sequence alignment). Tang et al. also teach methods of using said axotrophin polypeptide for regulating the growth and proliferation of T and/or B cells in a subject, and for treating graft-versus-host disease in a subject (See pg 44, line 15 through pg 51, line 14). Thus, the reference of Tang et al. meets all the limitations of claims 21-23.

Summary

23. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard, Ph.D.** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Manjunath N. Rao, Ph.D.**, can be reached on **(571) 272-0939**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon M. Lockard, Ph.D.
February 13, 2009

/Jon M Lockard/
Examiner, Art Unit 1647